REMARKS

Claims 1, 4-20, 23-32 and 38-40 are pending. Claims 1 and 20 are amended and claims 3 and 22 are cancelled herein. Claims 1 and 20 are amended to add the elements of claims 3 and 22, respectively.

35 U.S.C. § 102 Rejection

Reconsideration is respectfully requested of the rejection of claims 1, 7-9, 20, and 23-25 as anticipated by U.S. Patent No. 4,961,926 (Gabrilove) under 35 U.S.C. § 102(b). Claim 1 is directed to a method for reducing oral mucositis in a human or animal patient in need thereof exposed to radiation. The method comprises administering to the patient an effective amount of a protective agent selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, and a pharmaceutically acceptable salt thereof. The elements of previously presented claim 3 were added to claim 1. Claim 20 is similar to claim 1 but differs in that the patient is undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. The elements of previously presented claim 22 were added to claim 20. The Office found previously presented claims 3 and 22 patentable under 35 U.S.C. § 102(b) over Gabrilove.[1]

Gabrilove discloses methods of preventing mucositis comprising administering granulocyte colony stimulating factor (GCSF) or a polypeptide analog thereof. In particular, the GCSF analog may be a nonglycosylated polypeptide having an amino acid sequence identical to the sequence of the polypeptide component of naturally occurring GCSF (GCSF contains at least 144 amino acids) except for the presence of an additional methionine at the N-terminus. In one embodiment described in the Gabrilove reference, this 20,000 Dalton protein has one additional methionine residue to give a total of 145 amino acids. In contrast, the protectant agent claimed in claims 1 and 20 is D-methionine, L-methionine, and a mixture of D-methionine and L-methionine. Thus, Gabrilove does not anticipate claims 1, 7-9, 20, and 23-25 under 35 U.S.C. § 102(b).

[1] See Office action dated December 8, 2008 at page 2.

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 3-19, 22, 26-32 and 38-40 as unpatentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a).

Claims 1 and 4-19

Claim 3 is canceled and its elements incorporated into claim 1. Claims 4-19 depend directly or indirectly on claim 1 and incorporate all the elements of claim 1. Claim 1 is described in detail in connection with the § 102 rejection. The Office asserts that the only required element of claim 1 is that methionine is administered. Further, the Office admits that the Campbell reference does not expressly teach reducing mucositis but that Campbell does teach "administering D-methionine ... to reduce or ameliorate toxic side effects...."[2]

The Campbell reference describes methods for preventing or reducing ototoxicity, methods of preventing or reducing weight loss, methods of preventing or reducing gastrointestinal toxicity, methods of preventing or reducing neurotoxicity, and methods of preventing or reducing alopecia wherein all of these conditions arise from treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. As the Office further admits, the Campbell patent makes no mention of oral mucositis resulting from any type of insult; and that the patent provides no reason why D-methionine, L-methionine, or D,L-methionine (hereinafter "methionine") would have any value in dealing with oral mucositis resulting from radiation exposure or administration of an anti-tumor platinum-coordination compound.

First, the Office improperly construes the requirements of claim 1. Claim 1 requires (1) reducing oral mucositis in a human or animal patient in need thereof (2) exposed to radiation by (3) administering to the patient an effective amount of a protective agent selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, a pharmaceutically acceptable salt thereof, and a combination thereof. The Office improperly ignores the first and second requirements of the claim. Compare *Jansen v. Rexall Sundown, Inc.*[3]

[2] See Office action dated June 27, 2008 at page 4.
[3] 68 U.S.P.Q.2d 1154, 1158 (Fed. Cir. 2003).

where a claim directed to a "method of treating or preventing macrocytic-megaloblastic anemia in humans" by "administering a ... vitamin preparation to a human in need thereof...."[4] was construed by the Federal Circuit as follows.

> [T]he claims' recitation of a patient or a human "in need" gives life and meaning to the preambles' statement of purpose. *See Kropa v. Robie*, 187 F.2d 150, 152 [88 U.S.P.Q. 478] (C.C.P.A. 1951) (stating the rule that a preamble is treated as a limitation if it gives "life and meaning" to the claim). The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed.[5]

Thus, the preamble's requirement that the patient be exposed to radiation and in need of reduction of oral mucositis is an element that must be present in the cited references in order to negate patentability of claim 1.

Second, since the preamble must be given patentable weight, the issue is whether it would have been obvious to treat radiation-induced oral mucositis by administration of methionine. There can be no basis for inherency where the claim is directed to a method of treating a condition that ordinarily would not have been present in the patients whose treatment is described in the prior art; and there can be no basis for obviousness where the prior art further fails to recognize the potential effect of the treating agent against the condition specified in the claim. As the C.C.P.A has stated in reversing an obviousness rejection of a claim to a method of treating a specified condition with a defined treatment agent based on the inherent effect of treating a different condition with a similar agent.

> [Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty*.[6]

The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The *Shetty* court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was

[4] See id. at 1155.
[5] See id. at 1158.
[6] 195 U.S.P.Q. 753.

insufficient.[7] Similar to *Shetty*, claim 1 recites a method for reducing oral mucositis in a patient in need thereof exposed to radiation by administering methionine to said patient while the reference cited against these claims discloses methods for preventing or reducing ototoxicity, methods of preventing or reducing weight loss, methods of preventing or reducing gastrointestinal toxicity, methods of preventing or reducing neurotoxicity, and methods of preventing or reducing alopecia in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. Thus, claim 1 and the claims that depend therefrom are patentable over the cited references.

Moreover, the court in *Ex parte Zbornik* found a process for treating Air Sac Infection in fowl patentable over prior art disclosing substantially the same compound to treat ducks for malaria.[8] The *Zbornik* court found that the claims were patentable because the cited reference was not concerned with appellant's problem and it failed to suggest its solution. Similarly, the cited reference is concerned with preventing or reducing ototoxicity, preventing or reducing weight loss, preventing or reducing gastrointestinal toxicity, preventing or reducing neurotoxicity, and preventing or reducing alopecia in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound, and it fails to suggest to a skilled person that methionine would reduce oral mucositis in a patient exposed to radiation and in need of treatment.

Further, claim 1 and the claims that depend therefrom are patentable under 35 U.S.C. 103(a) over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) when evaluating non-obviousness per PTO Guidelines Under *KSR* as published in M.P.E.P. § 2143.

The Guidelines enumerate and explain seven separate grounds for finding obviousness under *KSR*. They are:

(A) combining prior art elements according to known methods to yield predictable results;

(B) simple substitution of one known element for another to yield predictable results;

(C) use of known technique to improve similar devices in the same way;

[7] See id. at 756.
[8] *Ex parte Zbornik*, 109 U.S.P.Q. 508.

(D) applying a known technique to a known device ready for improvement to yield predictable results;

(E) "obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) known work in one field of endeavor may prompt variations of it for use in the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; or

(G) some teaching, suggestion, or motivation in the art that would have led one of ordinary skill in the art to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Each ground requires several factual inquiries. In addition to other findings which vary among the seven separate grounds, each of them requires a finding of predictable results. Enumerated grounds (A) through (F) of the Guidelines all expressly require a showing of predictable results, while ground (G) is the conventional motivation test as applied by the Federal Circuit substantially since the inception of that court. The motivation test as laid out in Ground (G) also requires predictable results, expressed in terms of "a reasonable expectation of success."

For example, with respect to Ground (A), the evidence shows that each element is not merely performing the same function as it did separately. Instead the elements of administering methionine to reduce oral mucositis in a patient exposed to radiation and being in need of treatment is a new combination of the elements and methionine was not known from the cited references to reduce oral mucositis in a patient in need thereof and exposed to radiation. While methionine has been administered to patients for other purposes, the methionine was not administered to reduce oral mucositis in patients exposed to radiation and in need of treatment and from a contemplation of the cited art, it would not have been predictable that administration of methionine to reduce oral mucositis in a patient exposed to radiation and in need of treatment would have been beneficial.

With respect to Ground (B), the inventors did not merely substitute one element for another. For proper rejection on this ground, there must be a known and finite number of alternative elements to choose from and/or there must be known similarity in structure and function between the element required by the claim and that taught by the art. Neither is the case

here. There are vast differences between methionine and granulocyte colony stimulating factor (GCSF) with respect to both structure and known function. That GCSF contains a terminal methionine residue does not create a structural similarity that one skilled in the art would consider significant, and it would certainly fail to provide any basis for expectation of similar properties. Nor is there any art of record that suggests GCSF and methionine have any similarity in function for any relevant purpose. The patient population to be treated by the method was those patients exposed to radiation and in need of treatment for oral mucositis. It would not have been predictable from a contemplation of the prior art that administering methionine to a patient in need of treatment for oral mucositis would have provided a beneficial effect.

No basis other than hindsight could support the alternative perception that a patient suffering from radiation-induced mucositis should somehow be "substituted" in the method of Campbell for a patient suffering from the entirely different maladies for which methionine is administered in the Campbell method. One skilled in the art and concerned with treatment of radiation-induced mucositis would simply not have started with the method of Campbell.

The same applies to Ground (C). It makes no sense to start with a "base" method such as that disclosed by Campbell wherein methionine is used to prevent or reduce ototoxicity, prevent or reduce weight loss, prevent or reduce gastrointestinal toxicity, prevent or reduce neurotoxicity, and prevent or reduce alopecia in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. Nor does it make sense to start with Gabrilove which uses an entirely different treatment agent and therefore does not treat any condition in the same way as Campbell. In short, there is no evidence of any "comparable" method to treat oral mucositis that could have been improved by selection of methionine. Further, the advantageous effects of the administration of methionine for reducing oral mucositis in a patient exposed to radiation and in need of treatment would not have been predictable to a person of skill in the art from the cited references or knowledge in the art.

The analysis of Ground (D) is similar to that of Ground (C). In neither case could a base method have been selected to which a known technique could have been applied to achieve any predictable result. If Gabrilove were deemed a "known [process] ready for improvement," there is no basis in Campbell for substituting methionine for GCSF since Campbell has nothing to do with oral mucositis, the structures of methionine and GCSF are grossly different, one skilled in

the art would have expected their physiological effects to be entirely different, and one skilled in the art would not have known that methionine and GCSF shared any property relevant to the treatment of mucositis. Since Campbell has nothing to do with oral mucositis, there is simply no way that it could have been selected as the base method "ready for improvement;" and the substitution of a different condition for treatment cannot be construed as applying a "known technique." In any case, substituting the mucositis condition of Gabrilove for the conditions dealt with by Campbell could not have been obvious, and certainly the results would not have been predictable. Further, as in the case of Ground (C), the advantageous effects of the administration of methionine for reducing oral mucositis in a patient exposed to radiation and in need of treatment would not have been predictable to a person of skill in the art from the cited references or knowledge in the art.

There is no evidence of any measure that was "obvious to try" in support of Ground (E). Administration of methionine to a patient exposed to radiation and in need of treatment for oral mucositis was not known and was not "obvious to try." Further, there were not a finite number of solutions that could be varied with predictable results because the results were unpredictable.

As to Ground (F), there is no evidence that either the field of endeavor or a different field included an analogous method, at least not any method that is more relevant than that of Campbell. The differences between the method of claim 1 and Campbell were not encompassed by any known variations or in any principle known to the art. Assuming *arguendo* that it was known that methionine treated side effects of various treatments, there was no known variation or principle which suggested that a patient exposed to radiation and in need of treatment for oral mucositis would have benefitted from the administration of methionine.

As noted, Ground (G) is the conventional motivation test as long applied by the Federal Circuit. There was no motivation in the art to administer methionine to a patient exposed to radiation and in need of treatment for oral mucositis. Although the side effect of oral mucositis in patients receiving radiation treatments for various conditions was known, the art did not suggest a way to alleviate oral mucositis that was in any way comparable to the instantly claimed method. Thus, there was no teaching, motivation or suggestion in the art to try methionine or any amino acid as a treatment for mucositis. Further, there was not a reasonable expectation that administration of methionine to a patient exposed to radiation and in need of treatment for oral mucositis would have had a beneficial effect.

Moreover, there is no reason provided why a skilled person would have substituted methionine as disclosed by Kil for the GCSF protein of Gabrilove to treat oral mucositis resulting from radiation exposure. A skilled person would have attributed the anti-mucositis effect of the GCSF protein to the specific structural aspects of the protein and not solely or primarily to the presence of an additional methionine residue at the N-terminus. From the Gabrilove disclosure, a skilled person would have learned that recombinant hG-CSF (rhG-CSF) is "a specific growth and differentiation factor for neutrophil granulocytes"[9] and that "recombinant hG-CSF may reduce the incidence of mucositis by enhancing the number of neutrophils, as well as their functional capability to guard the mucosal barriers more efficiently."[10] From these statements, a skilled person would have known that the primary, secondary, and tertiary structure of the 20,000 Dalton rhG-CSF protein was instrumental in its neutrophil granulocyte growth stimulation and mucositis protection functions.

A skilled person would not have expected D-methionine, L-methionine, or D,L-methionine, a 150 Dalton small molecule amino acid, to provide the same physiological effect as the 20,000 Dalton GCSF protein, regardless of whether an additional methionine unit happens to be present at the N-terminus of the protein. Even if it were assumed that an additional methionine at the N-terminus of the GCSF protein is somehow instrumental in imparting significant properties to the protein as a whole, one skilled in the art would scarcely expect that the monomeric amino acid by itself would provide a comparable effect. By way of example, proteins, including GCSF proteins act upon cell components through various chemical and physical interactions. In particular, the primary, secondary, and tertiary (e.g., three dimensional) structure of the protein including surfaces for binding and interacting with various molecules is well known to be essential to the biological function which the protein exhibits. A protein can also undergo various conformational changes upon binding a molecule at a particular binding site. Monomeric methionine does not have the same type of complex three-dimensional structure and would not be expected to stimulate growth of neutrolphil granulocytes. Thus, a person of ordinary skill would not have expected methionine by itself to be an effective agent against oral mucositis based on the Gabrilove disclosure alone or as combined with the Campbell disclosure.

[9] See U.S. Patent No. 4,961,926, column 2, lines 41 to 43.
[10] See U.S. Patent No. 4,961,926, column 7, line 67 to column 8, line 14.

Kil et al. does not remedy the deficiencies of Campbell or Gabrilove. Kil et al. teach combinations of chemoprotectants that ameliorate at least one side effect of chemotherapy. However, like the Campbell patent, Kil et al. makes no mention of mucositis resulting from any type of insult; and provides no reason why D-methionine, L-methionine, or D,L-methionine would have any value in dealing with oral mucositis resulting from radiation exposure. Thus, there was no basis in Campbell, Gabrilove or Kil for combining their teachings in any manner, or for selecting either Campbell or Kil as sources of learning for modifying, in this case drastically modifying, the method of Gabrilove. As explained above for the combination of the Campbell patent and Gabrilove, even if Campbell, Gabrilove, and Kil were read together, they would not have provided a reason to combine their respective and disparate teachings, and even if the teachings were combined, the combination would not have led a person of ordinary skill to find the present claims for reducing oral mucositis using the small molecule methionine obvious for at least the same reasons as described above for the Campbell and Gabrilove combination. Further, as described for the Campbell and Gabrilove combination, a person of ordinary skill would not have expected methionine by itself to be an effective agent against oral mucositis based on the combination of Campbell, Gabrilove, and Kil disclosures.

Further with respect to the position stated in the instant Office action on the scope of a protective agent "comprising ... methionine," the GCSF protein of Gabrilove does not "comprise" methionine, which is an amino acid, but rather contains a peptide unit which is the residue of methionine, not the amino acid itself.

In order to further distinguish the amino acid protective agents encompassed by the instant claims from the GCSF protein, the instant amendment limits the protective agent to "D-methionine, L-methionine, or D,L-methionine," each of which unambiguously denotes a monomeric amino acid and therefore does not read on GCSF protein, or any other protein or peptide.

Applicant respectfully reserves the right to pursue a continuation application which claims the method in the terms stated in the claims prior to the instant amendment.

Claims 20 and 26-32

Claims 26-32 depend on claim 20. The elements of claim 22 were incorporated into claim 20. Claim 20 is described in detail in connection with the § 102 rejection.

Similar to claim 1, the Office improperly construes the requirements of claim 20. Claim 20 requires (1) reducing oral mucositis in a human or animal patient in need thereof (2) undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound by (3) administering to the patient an effective amount of a protective agent selected from the group consisting of D-methionine, L-methionine, a mixture of D-methionine and L-methionine, a pharmaceutically acceptable salt thereof, and a combination thereof. Although the Office ignores the first requirement of the claim, as discussed above, the *Jansen* court found that the preamble stated a positive element of the claim which must be met by the art in order to sustain a rejection. Thus, the preamble's requirement that reducing oral mucositis in a human or animal patient in need thereof and the patient is undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound are elements that must be present in the cited references in order to negate patentability of claim 20.

The Campbell reference is described above. Since the preamble must be given patentable weight, the issue is whether it would have been obvious to treat oral mucositis caused by an anti-tumor platinum-coordination compound with methionine. As described above, inherency is not material in this factual situation. Similar to *Shetty*, claim 20 recites a method for reducing oral mucositis in a patient in need thereof undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound by administering methionine to said patient. This provides a sharp patentable difference from the reference cited against these claims which discloses entirely different methods, i.e., methods for preventing or reducing ototoxicity, methods of preventing or reducing weight loss, methods of preventing or reducing gastrointestinal toxicity, methods of preventing or reducing neurotoxicity, and methods of preventing or reducing alopecia in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. Thus, claim 20 and the claims that depend therefrom are patentable over the cited references.

Moreover, as described above, the court in *Ex parte Zbornik* found a process for treating Air Sac Infection in fowl patentable over prior art disclosing substantially the same compound to treat ducks for malaria.[11] Similarly, the cited reference is concerned with preventing or reducing ototoxicity, preventing or reducing weight loss, preventing or reducing gastrointestinal toxicity,

[11] *Ex parte Zbornik*, 109 U.S.P.Q. 508.

preventing or reducing neurotoxicity, and preventing or reducing alopecia in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound, and it fails to suggest to a skilled person that methionine would reduce oral mucositis in a patient in need thereof undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound.

Further, claim 20 and the claims that depend therefrom are patentable under 35 U.S.C. 103(a) over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) when evaluating non-obviousness per PTO Guidelines Under *KSR* as published in M.P.E.P. § 2143.

The seven separate grounds explained in the Guidelines are described above. When applying them to claim 20, for example, with respect to Ground (A), the evidence shows that each element is not merely performing the same function as it did separately. Instead the elements of administering methionine to reduce oral mucositis in a patient in need thereof undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound is a new combination of the elements and methionine was not known from the cited references to reduce oral mucositis in a patient in need thereof undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. While methionine has been administered to patients for other purposes, the methionine was not administered to reduce oral mucositis in patients in need thereof undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound and from a contemplation of the cited art, it would not have been predictable that administration of methionine to reduce oral mucositis in a patient in need thereof undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound would have been beneficial.

With respect to Ground (B), the inventors did not merely substitute one element for another. The patient population to be treated by the method was those patients in need of treatment for oral mucositis and undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. It would not have been predictable from a contemplation of the prior art that administering methionine to a patient in need of treatment for oral mucositis would have been beneficial.

With regard to Ground (C), the "base" method would be the method of Campbell. There is no evidence of any "comparable" method which was improved by selection of methionine to treat oral mucositis. Such a selection would not have provided predictability as to its advantageous effects for oral mucositis.

The analysis of Ground (D) is similar to that of Ground (C). The base method would be the same in both cases. There is no evidence that the prior art contained a known method of administering methionine, or any other agent similar in structure or known properties, to a patient in need of treatment for oral mucositis and undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound.

There is no evidence of any measure that was "obvious to try" in support of Ground (E). Administration of methionine to a patient in need of treatment for oral mucositis and undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound was not known and was not "obvious to try." Further, there were not a finite number of solutions that could be varied with predictable results because the results were unpredictable.

As to Ground (F), there is no evidence that either the field of endeavor or a different field included an analogous method, at least not any method that is more relevant than that of Campbell. The differences between the method of claim 1 and Campbell were not encompassed by any known variations or in any principle known to the art. Assuming *arguendo* that it was known that methionine treated side effects of various treatments, there was no known variation or principle which suggested that a patient in need of treatment for oral mucositis and undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound would have benefitted from the administration of methionine.

As noted, Ground (G), is the conventional motivation test as long applied by the Federal Circuit. There was no motivation in the art to administer methionine to a patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound and in need of treatment for oral mucositis. Although the side effect of oral mucositis in patients undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound were known, the art did not suggest a way to alleviate oral mucositis that was in any way comparable to the instantly claimed method. Thus, there was no teaching, motivation or suggestion in the art to try methionine or any amino acid as a treatment for mucositis.. Further, there was not a reasonable expectation that administration of methionine

to a patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound and in need of treatment for oral mucositis would have been beneficial.

Moreover, there is no reason provided why a skilled person would have substituted methionine as disclosed by Kil for the GCSF protein of Gabrilove to treat oral mucositis resulting from administration of an anti-tumor platinum-coordination compound. A skilled person would have attributed the anti-mucositis effect of the GCSF protein to the specific structural aspects of the protein and not solely or primarily to the presence of an additional methionine residue at the N-terminus. From the Gabrilove disclosure, a skilled person would have learned that recombinant hG-CSF (rhG-CSF) is "a specific growth and differentiation factor for neutrophil granulocytes"[12] and that "recombinant hG-CSF may reduce the incidence of mucositis by enhancing the number of neutrophils, as well as their functional capability to guard the mucosal barriers more efficiently"[13]. From these statements, a skilled person would have known that the primary, secondary, and tertiary structure of the 20,000 Dalton rhG-CSF protein was instrumental in its neutrophil granulocyte growth stimulation and mucositis protection functions.

A skilled person would not have expected D-methionine, L-methionine, or a mixture of D- and L-methionine, a 150 Dalton small molecule amino acid, to provide the same physiological effect as the 20,000 Dalton GCSF protein, regardless of whether an additional methionine unit happens to be present at the N-terminus of the protein. Even if it were assumed that an additional methionine at the N-terminus of the GCSF protein is somehow instrumental in imparting significant properties to the protein as a whole, one skilled in the art would scarcely expect that the monomeric amino acid by itself would provide a comparable effect. By way of example, proteins, including GCSF proteins act upon cell components through various chemical and physical interactions. In particular, the primary, secondary, and tertiary (e.g., three dimensional) structure of the protein including surfaces for binding and interacting with various molecules is well known to be essential to the biological function which the protein exhibits. A protein can also undergo various conformational changes upon binding a molecule at a particular binding site. Monomeric methionine does not have the same type of complex three-dimensional

[12] See U.S. Patent No. 4,961,926, column 2, lines 41 to 43.
[13] See U.S. Patent No. 4,961,926, column 7, line 67 to column 8, line 14.

structure, and would not be expected to stimulate growth of neutrolphil granulocytes. Thus, a person of ordinary skill would not have expected methionine by itself to be an effective agent against oral mucositis based on the Gabrilove disclosure alone or as combined with the Campbell disclosure.

Kil et al. does not remedy the deficiencies of Campbell or Gabrilove. Kil et al. teach combinations of chemoprotectants that ameliorate at least one side effect of chemotherapy. However, like the Campbell patent, Kil et al. makes no mention of mucositis resulting from any type of insult; and provides no reason why D-methionine, L-methionine, or a mixture of D- and L-methionine would have any value in dealing with oral mucositis resulting from administration of an anti-tumor platinum-coordination compound. Thus, there was no basis in Campbell, Gabrilove or Kil for combining their teachings in any manner, or for selecting either Campbell, or Kil as sources of learning for drastically modifying the method of Gabrilove. As explained above for the combination of the Campbell patent and Gabrilove, even if Campbell, Gabrilove, and Kil were read together, they would not have provided a reason to combine their respective and disparate teachings, and even if the teachings were combined, the combination would not have led a person of ordinary skill to find the present claims for reducing oral mucositis using the small molecule methionine obvious for at least the same reasons as described above for the Campbell and Gabrilove combination. Further, as described for the Campbell and Gabrilove combination, a person of ordinary skill would not have expected methionine by itself to be an effective agent against oral mucositis based on the combination of Campbell, Gabrilove, and Kil disclosures.

Further, while oral mucositis may be an effect of chemotherapy, oral mucositis resulting from treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound occurs in fewer patients than other side effects such as, for example, ototoxicity, neurotoxicity, weight loss, and alopecia. Specifically, the cisplatin dosages exemplified in the Campbell patent and Kil reference would not inevitably have resulted in oral mucositis. Thus, a patient receiving treatment with an anti-tumor platinum-coordination compound could develop ototoxicity, neurotoxicity, weight loss, and alopecia, and not inevitably develop oral mucositis. This pattern of side effects shows the variations in mechanism of damage to cells in different tissues. Since there is no basis for one skilled in the art to know that oral mucositis was actually suffered by any subject exposed to cisplatin as described by Campbell or Kil, there is no basis for

one skilled in the art to infer that any subject suffering from oral mucositis was ever treated with methionine according to either the Campbell or Kil experimental protocols. Much less is there anything in these references that would lead one skilled in the art to believe that methionine treatment might have been effective to control oral mucositis, or that it ever could be. Thus, the unpredictability of the side effects, combined with absence of any teaching that methionine might be effective against oral mucositis from any source, would have foreclosed any reasonable expectation that methionine would have been effective to ameliorate oral mucositis resulting from administration of an anti-tumor platinum-coordination compound.

Claims 38-40

Reconsideration is respectfully requested of the rejection of claims 38-40 as unpatentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a). Claim 38 is dependent on claim 1 and directed to a method of treating oral mucositis wherein the patient is exposed to radiation and is undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound. Thus, claims 38-40 are patentable over U.S. Patent No. 6,187,817 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove) and further in view of WO 03/045334 (Kil et al.) under 35 U.S.C. § 103(a) for at least the same reasons as claim 1.

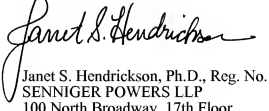
It is respectfully submitted that the Office has failed to establish obviousness based on the cited references or by evidence of the level of skill in the art or the nature of the problem that is not based upon impermissible hindsight reconstruction. Thus, claims 1, 4-19, 20, 26-32 and 38-40 are patentable over the cited references.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



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